

We claim:

1. A method of inducing a T-cell response to a tumor that overexpresses mesothelin relative to normal tissue from which the tumor is derived, said method comprising:
administering to a patient who has said tumor or who has had said tumor removed, a vaccine comprising a polypeptide comprising an MHC Class I-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I which is expressed by the patient, whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.
2. The method of claim 1 wherein the tumor is selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, and squamous cell carcinoma.
3. The method of claim 1 wherein the tumor is a pancreatic cancer.
4. The method of claim 1 wherein the tumor is an ovarian cancer.
5. The method of claim 1 wherein epitope is selected from the group consisting of: SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLC SL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
6. The method of claim 1 wherein the polypeptide is mature mesothelin.
7. The method of claim 1 wherein the polypeptide is the primary translation product of mesothelin.
8. The method of claim 1 wherein a mixture of said polypeptides is administered.
9. The method of claim 8 wherein said polypeptides bind to a plurality of allelic forms of MHC Class I molecules.
10. The method of claim 8 wherein said polypeptides bind to a single allelic form of MHC Class I molecules.
11. The method of claim 1 wherein the polypeptide is selected as being an MHC class I-binding epitope using an algorithm.
12. The method of claim 1 wherein the polypeptide is selected as being an MHC class I-binding epitope using two algorithms.
13. The method of claim 1 wherein the T-cell response is induction of specific CD8⁺ T cells.
14. The method of claim 1 wherein the vaccine is acellular.
15. The method of claim 1 wherein the vaccine comprises a bacterium selected from the group consisting of: *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.

16. The method of claim 1 wherein the vaccine is administered in sufficient amount to induce tumor regression.
17. The method of claim 1 wherein the vaccine is administered in sufficient amount to keep the patient tumor-free after removal of the tumor.
18. A method of inducing a T-cell response to a tumor that overexpresses mesothelin relative to normal tissue from which the tumor is derived, said method comprising:
 - administering to a patient who has said tumor or who has had said tumor removed, a vaccine comprising a polypeptide comprising an MHC Class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class II which is expressed by the patient, whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.
19. A method of inducing a T-cell response to tumor cells that overexpress mesothelin relative to normal cells from which the tumor cells are derived, said method comprising:
 - administering to a patient who is at risk of developing a tumor that overexpresses mesothelin a vaccine comprising a polypeptide comprising an MHC class I-binding epitope of mesothelin or an MHC class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I or class II which is expressed by the patient, whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.
20. The method of claim 19 wherein the patient has been exposed to a carcinogen which is known to induce tumors which overexpress mesothelin relative to normal tissue from which the tumor is derived.
21. The method of claim 20 wherein the carcinogen is asbestos.
22. A method of inducing a T-cell response to a tumor which overexpresses mesothelin relative to normal tissue from which it is derived, said method comprising:
 - administering to a patient who has said tumor or who has had said tumor removed, a vaccine comprising a polynucleotide encoding a polypeptide comprising an MHC Class I-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I which is expressed by the patient, whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.
23. The method of claim 22 wherein the tumor is selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, and squamous cell carcinoma.
24. The method of claim 22 wherein the tumor is a pancreatic cancer.

25. The method of claim 22 wherein the tumor is an ovarian cancer.
26. The method of claim 22 wherein epitope is selected from the group consisting of:
SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and
LYPKARLAF (SEQ ID NO: 6).
27. The method of claim 22 wherein the polypeptide is mature mesothelin.
28. The method of claim 22 wherein the polypeptide is primary translation product of mesothelin.
29. The method of claim 22 wherein the vaccine comprises one or more polynucleotides encoding a mixture of said polypeptides.
30. The method of claim 29 wherein said polypeptides bind to a plurality of allelic forms of MHC Class I molecules.
31. The method of claim 29 wherein said polypeptides bind to a single allelic form of MHC Class I molecules.
32. The method of claim 22 wherein the polypeptide is selected as being an MHC class I-binding epitope using an algorithm.
33. The method of claim 22 wherein the polypeptide is selected as being an MHC class I-binding epitope using two algorithms.
34. The method of claim 22 wherein the T-cell response is induction of specific CD8⁺ T cells.
35. The method of claim 22 wherein the vaccine is acellular.
36. The method of claim 22 wherein the vaccine comprises a bacterium selected from the group consisting of: *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.
37. The method of claim 22 wherein the vaccine is administered in sufficient amount to induce tumor regression.
38. The method of claim 22 wherein the vaccine is administered in sufficient amount to keep the patient tumor-free after removal of the tumor.
39. A method of inducing a T-cell response to a tumor that overexpresses mesothelin relative to normal tissue from which the tumor is derived, said method comprising:
administering to a patient who has said tumor or who has had said tumor removed, a vaccine comprising a polynucleotide encoding a polypeptide comprising an MHC Class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class II which is expressed by the patient,

whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.

40. A method of inducing a T-cell response to tumor cells that overexpress mesothelin relative to normal cells from which the tumor cells are derived, said method comprising:
administering to a patient who is at risk of developing a tumor that overexpresses mesothelin a vaccine comprising a polynucleotide encoding a polypeptide comprising an MHC class I-binding epitope of mesothelin or an MHC class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I or class II which is expressed by the patient, whereby a T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells.
41. The method of claim 40 wherein the patient has been exposed to a carcinogen which is known to induce tumors which overexpress mesothelin relative to normal tissue from which the tumor is derived.
42. The method of claim 41 wherein the carcinogen is asbestos.
43. A method of identifying immunogens useful as candidates for anti-tumor vaccines, comprising:
selecting a protein which is expressed by a tumor and which is minimally or not expressed by normal tissue from which the tumor is derived;
testing lymphocytes of humans who have been vaccinated with a vaccine which comprises said protein to determine if said lymphocytes comprise CD8⁺ T cells or CD4⁺ T cells which are specific for said protein, wherein the presence of said CD8⁺ T cells or CD4⁺ T cells indicates that the protein is a candidate for use as an anti-tumor vaccine.
44. The method of claim 43 wherein said humans have exhibited an anti-tumor immune response.
45. The method of claim 43 wherein the vaccine comprises whole tumor cells.
46. The method of claim 44 wherein the anti-tumor immune response results in prolonged disease-free survival post-surgical tumor removal relative to a similar population which has not been vaccinated.
47. The method of claim 44 wherein the anti-tumor immune response results in tumor regression.
48. The method of claim 44 wherein the anti-tumor immune response results in prolonged survival time.

49. The method of claim 44 wherein the anti-tumor immune response is delayed type hypersensitivity to autologous tumor cells.
50. The method of claim 43 wherein said lymphocytes are also tested to determine if they comprise CD8⁺ T cells or CD4⁺ T cells specific for an antigen not expressed by the vaccine.
51. The method of claim 43 wherein the humans are divided into two groups based on their response to the vaccine, wherein a first group comprises responders and a second group comprises non-responders, wherein if said CD8⁺ T cells or CD4⁺ T cells are found more frequently in responders than in non-responders then the protein is identified as more likely to be useful in an anti-tumor vaccine.
52. The method of claim 51 wherein responders display a DTH response to autologous tumor cells but non-responders do not display the response.
53. The method of claim 51 wherein responders have a longer period of disease free survival than non-responders.
54. A method of predicting future response to a tumor vaccine comprising at least one T-cell epitope of mesothelin in a patient who has received the vaccine, comprising:
 - testing lymphocytes of the patient to determine if the lymphocytes comprise CD8⁺ T cells or CD4⁺ T cells which are specific for mesothelin, wherein the presence of said CD8⁺ T cells or CD4⁺ T cells predicts a longer survival time than the absence of said CD8⁺ T cells.
55. The method of claim 54 wherein the vaccine comprises whole tumor cells.
56. The method of claim 54 wherein the vaccine comprises pancreatic tumor cells and the antigen is mesothelin.
57. The method of claim 54 wherein the vaccine comprises ovarian tumor cells and the antigen is mesothelin.
58. The method of claim 54 wherein the vaccine comprises mesothelioma cells and the antigen is mesothelin.
59. A vaccine which induces a CD8⁺ T cell or CD4⁺ T cell response, comprising:
 - a polypeptide comprising an MHC Class I- or Class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I of class II which is expressed by the patient, whereby a CD8⁺ T cell or CD4⁺ T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells; and
 - a carrier for stimulating a CD8⁺ T cell or CD4⁺ T cell immune response.

60. The vaccine of claim 59 wherein the polypeptide comprises an MHC Class I-binding epitope.
61. The vaccine of claim 59 wherein the polypeptide comprises between 6 and 20 amino acid residues.
62. The vaccine of claim 59 wherein the polypeptide comprises an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
63. The vaccine of claim 59 wherein the carrier is CD40/CD40 ligand.
64. The vaccine of claim 59 wherein the carrier is OX-40/OX-40 ligand.
65. The vaccine of claim 59 wherein the carrier is a CTLA-4 antagonist.
66. The vaccine of claim 59 wherein the carrier is GM-CSF.
67. A vaccine which induces a CD8⁺ T cell or CD4⁺ T cell response, comprising:
 - a polynucleotide encoding a polypeptide comprising an MHC Class I- or Class II-binding epitope of mesothelin, wherein the epitope binds to an allelic form of MHC class I or Class II which is expressed by the patient, whereby a CD8⁺ T cell or CD4⁺ T-cell response to mesothelin is induced, wherein the vaccine does not comprise whole tumor cells; and
 - a carrier for stimulating a CD8⁺ T cell or CD4⁺ T cell immune response.
68. The vaccine of claim 67 wherein the carrier is CD40/CD40 ligand.
69. The vaccine of claim 67 wherein the carrier is OX-40/OX-40 ligand.
70. The vaccine of claim 67 wherein the carrier is a CTLA-4 antagonist.
71. The vaccine of claim 67 wherein the carrier is GM-CSF.
72. The vaccine of claim 67 wherein the polypeptide comprises an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
73. The vaccine of claim 59 which comprises a bacterium.
74. The vaccine of claim 67 which comprises a bacterium.
75. The vaccine of claim 73 wherein the bacterium is selected from the group consisting of : *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.

76. The vaccine of claim 74 wherein the bacterium is selected from the group consisting of : *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.
77. An isolated polypeptide of 9 to 25 amino acid residues comprising an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
78. A fusion protein comprising a first and a second portion, wherein the first portion comprises a polypeptide of 9 to 25 amino acid residues comprising an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6), and the second portion comprises a segment of at least 6 amino acid residues, wherein the sequence of said second portion is not in mesothelin.
79. An expression vector which encodes a polypeptide of 9 to 25 amino acid residues comprising an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
80. A bacterium which comprises the expression vector of claim 79.
81. The bacterium of claim 80 which is selected from the group consisting of *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.
82. An expression vector which encodes the fusion protein of claim 78.
83. A bacterium which comprises the expression vector of claim 82.
84. The bacterium of claim 83 which is selected from the group consisting of *Shigella flexneri*, *E. coli*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Salmonella typhi*, and mycobacterium.
85. An isolated antibody that binds to an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3); ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).
86. A T-cell line that binds to an epitope selected from the group consisting of SLLFLLFSL (SEQ ID NO: 1); VLPLTVAEV (SEQ ID NO: 2); ELAVALAQK (SEQ ID NO: 3);

ALQGGGPPY (SEQ ID NO: 4); FYPGYLCSL (SEQ ID NO: 5); and LYPKARLAF (SEQ ID NO: 6).

87. The polypeptide of claim 77 which is bound to an MHC Class I molecule.
88. The fusion protein of claim 78 which is bound to an MHC Class I molecule.
89. The vaccine of claim 59 wherein the carrier is an MHC Class I molecule.
90. The polypeptide of claim 87 wherein the MHC Class I molecule is on a dendritic cell.
91. The fusion protein of claim 88 wherein the MHC Class I molecule is on a dendritic cell.
92. The vaccine of claim 89 wherein the MHC Class I molecule is on a dendritic cell.
93. The polypeptide of claim 87 wherein the MHC Class I molecule is on an antigen presenting cell.
94. The polypeptide of claim 88 wherein the MHC Class I molecule is on an antigen presenting cell.
95. The vaccine of claim 89 wherein the MHC Class I molecule is on an antigen presenting cell.
96. A method of predicting future response to a tumor vaccine in a patient who has received the vaccine, comprising:
 - testing the patient to determine if the patient has a delayed type hypersensitivity (DTH) response to mesothelin, wherein the presence of said response predicts a longer survival time than the absence of said response.
97. The method of claim 96 wherein the vaccine comprises whole tumor cells.
98. The method of claim 96 wherein the vaccine comprises pancreatic tumor cells.
99. The method of claim 96 wherein the vaccine comprises ovarian tumor cells.
100. The method of claim 96 wherein the vaccine comprises mesothelioma cells.
101. A recombinant mouse cell line which comprises peritoneal cells which have been transformed by HPV-16 E6 and E7 and an activated oncogene wherein the cell line is capable of forming ascites and tumors upon intraperitoneal injection into an immunocompetent mouse.
102. The recombinant mouse cell line of claim 101 wherein the activated oncogene is an activated c-Ha-ras.
103. The recombinant mouse cell line of claim 101 which expresses mesothelin.
104. The recombinant mouse cell line of claim 101 which is WF-3.
105. A mouse model comprising:
 - a mouse which has been injected with the recombinant mouse cell line of claim 101.

106. The mouse model of claim 105 which is immunocompetent.
107. A method of testing a substance to determine if it is a potential drug for treating a cancer selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, and squamous cell carcinoma, comprising:
contacting the mouse model of claim 105 with a test substance; and
determining if the test substance causes regression of a tumor in the mouse model, diminution of ascites volume in the mouse model, or longer survival time in the mouse model.
108. A method of testing a substance to determine if it is a potential drug for treating a cancer selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, and squamous cell carcinoma, comprising:
contacting a mouse with a test substance;
injecting the mouse with the recombinant cell line of claim 101, and
determining if the test substance causes regression of a tumor in the mouse, diminution of ascites volume in the mouse, or longer survival time in the mouse.
109. The vaccine of claim 59, wherein the polypeptide is mesothelin.
110. The method of claim 1, wherein the polypeptide is mesothelin.
111. The method of claim 22, wherein the polypeptide is mesothelin.
112. The vaccine of claim 67, wherein the polypeptide is mesothelin.